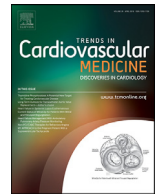




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## Editorial commentary: Long COVID-19: A tangled web of lungs, heart, mind, and gender

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After more than 1 year after the initial pandemic wave of SARS-CoV-2 infection, the consequences of coronavirus disease (COVID-19) are still affecting healthcare systems worldwide and overwhelming local medical resources. Beyond the well-known complications related to COVID-19 in the acute phase of infection, a growing body of evidence is emerging about the implications of prolonged symptoms called “long COVID” [1,2]. Along with dyspnea and persistent respiratory impairment, up to 25% of recovered patients complain of anxiety or depression several weeks or months following the onset of symptoms suggestive of COVID-19 [3]. Compared to the estimates before COVID-19 outbreak, epidemiological data suggest that COVID-19 confers 7-fold increased risk of developing depression and mental health issues [4].

While understudied, the association between global pandemic and mental illness has been described in past pandemics for over a century. Survivors of the Russian influenza pandemic of 1889 reported years of fatigue, insomnia, depression, anxiety, and psychoses [5]. Similarly, in the 6 years following the Spanish flu pandemic of 1918, first-time asylum hospitalizations in Norway with mental disorders attributed to influenza increased by an average annual factor of 7.2 [6]. Survivors of Spanish flu were also reported to have increased rates of sleep disturbances, depression, difficulties coping at work, and suicide [7]. In more contemporary times, following the 2003 SARS CoV-1 pandemic in Hong Kong, there was a 32% increase in suicide rates, and survivors of SARS had persistently elevated stress and psychological distress levels [8,9]. Interestingly, in the prior pandemic literature, there has not been a consistent association between gender and pandemic-related mental illness.

There are inherent sex differences that have been noted in the pathophysiology of COVID-19 infection as Bucciarelli et al. [10] elegantly detailed in their review. While men tend to have higher severity and fatality rates in COVID-19 infection [11], women, especially middle-age women, are significantly more likely to develop long COVID [12]. Although the exact mechanisms are not clear yet, a persistent subclinical inflammatory hypothesis associated with an autoimmune reaction are thought to partially explain the higher incidence of this syndrome among women [13–15]. Other potential etiologies include unmasking of comorbidities, residual damage

from acute infection, and persistent viral replication [16]. Several of long COVID symptoms share similar characteristics with those of patients with mental illness including depression, fatigue, or generalized weakness [17], and, of course, depression by itself has long been associated with cardiovascular disease [18]. Thus, along with the mental health related symptoms, long COVID-19 may ultimately represent a key substrate for an increased risk of cardiovascular (CV) disease.

Additionally, as previously noted during the Ebola virus and the Zika virus outbreaks [19,20], women experience larger financial issues and consequent chronic stress due to their primary employment in economic sectors more affected by social distancing which significantly suffered from the outbreak restrictions. Changes in lifestyle, isolation at home, along with the aforementioned mental health issues, promote an increase in sedentary time and a negative dietary pattern. Unhealthy behaviors and the combined effect of a proactive inflammatory substrate due to long COVID-19 syndrome, may therefore represent relevant CV risk factors with a potential impact on prognosis. From this perspective, cardiac rehabilitation programs should be encouraged to mitigate the mental health consequences of COVID-19 and to prevent the deleterious effects on the CV system. Ultimately, these data highlight the need for a proactive approach to follow-up affected patients with a systematic assessment to include symptoms of mental and physical health and to promote specific healthcare programs to support healthier lifestyle and trained physical activity after COVID-19 infection.

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